

Advanced contrasts for vascular MRI

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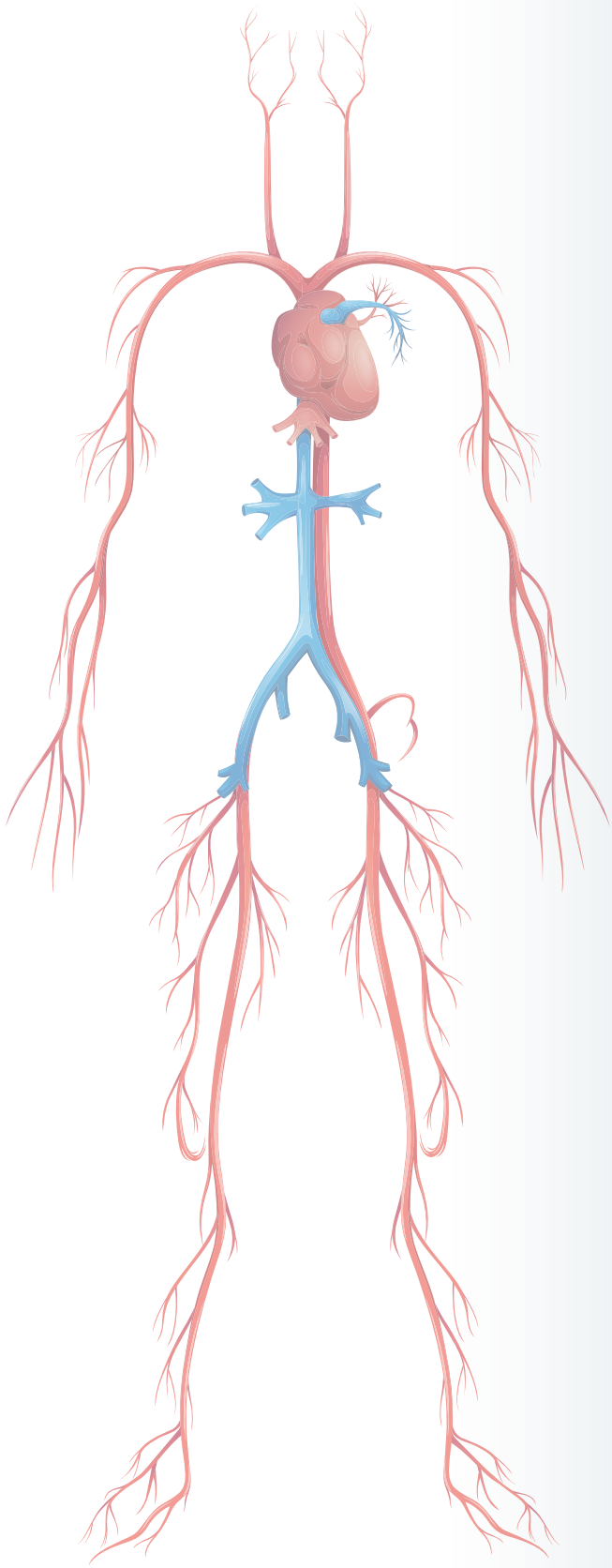
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VALORISATION

Relevance of the study

Clinical healthcare problem

Diseases of the heart and blood vessels, so-called cardiovascular diseases, are the number one cause of death worldwide. The World Health Organization estimated that 17.5 million people died from cardiovascular diseases in 2012. In the Netherlands, 8.3 billion euro was spent on the treatment of cardiovascular diseases in 2011, which was 9.2% of the total health care costs. By minimizing behavioral risk factors such as alcohol and tobacco use, obesity, unhealthy diet and physical inactivity, the risk for cardiovascular diseases can be reduced, but not eliminated. Patients who already developed clinical symptoms or have more than one cardiovascular risk factor may benefit from cardiovascular imaging by early detection of cardiovascular disease and identification of the disease stage, followed by appropriate treatment.

Diagnostic imaging of cardiovascular disease should, like every diagnostic test, have a high sensitivity and specificity. Ideally, the method is fast and should be able to identify early signs of cardiovascular disease, in a stage where the disease process may still be reversible. Examples of abnormal pathophysiology of the vascular system that can be imaged include atherosclerosis, which is a main underlying cause of myocardial infarction, cerebrovascular stroke and abnormal vessel development, and angiogenesis, which is an indication of disease progression in malignant tumors.

The current clinical angiographic techniques are able to visualize the large blood vessels very well. With or without contrast enhancement these techniques depict the lumen of the blood vessels (luminography). However, diagnosing the pathophysiology of the vascular disease is limited, as for instance the age of the thrombus that caused a cerebrovascular stroke or the degree of tumor angiogenesis, cannot be determined. To enable a next step in cardiovascular diagnosis, and to facilitate personalized treatment and monitoring of therapeutic responses, molecular markers may play a big role by specifically concentrating of contrast media to the pathophysiologic site. The same technology might be used to direct therapeutic agents, ideally combined with a diagnostic agent, an approach commonly referred to as theragnostics. The current clinically available nuclear imaging techniques, which are based on targeting of radioactively labeled molecular markers, are already highly suitable to visualize alterations in receptor expression, but do not provide a detailed anatomical (soft-tissue) image. To address this problem, clinical hybrid PET/CT and PET/MRI systems have been introduced. Such hybrid imaging modalities enable a single-stop-exam for the patient. However, a disadvantage of these nuclear imaging modalities is the need for radioactive pharmaceuticals, which makes it less suitable for screening and repeated follow-up studies. Therefore, there is a need for other approaches in diagnostic vascular imaging, for which MRI seems an ideal candidate. MRI does not use ionizing radiation, provides excellent soft tissue contrast and, in theory, is capable of using different types of contrast media to localize different molecular markers. Gadolinium-based contrast agents (GBCAs) are commonly used due to their good contrast enhancement and the relative low risks of adverse side effects. However, GBCAs cannot be used in patients with severely impaired kidney function because of the risk of nephrogenic systemic fibrosis (NSF). In addition, depositions of GBCAs in the brain and bones of patients,

even those with normal renal function, were documented, although no short or long-term adverse effects of the low concentration of the deposition have been observed yet [1-3]. Furthermore, contrast enhancement properties of GBCAs are not optimal for molecular MRI. Novel concepts of contrast media and associated advanced MR imaging techniques are needed for molecular MRI.

Approach

For MR angiography, different methods are available to increase the contrast between the vascular lumen and surrounding tissue. In addition, molecular MRI can highlight disease-specific molecular targets of the vascular wall. Despite the wide clinical use of GBCAs, other MR contrast media could have specific advantages for vascular MRI. In certain applications such as imaging small objects like small blood vessels, or when the target tissue region is very small and hypodense as in some molecular imaging applications, the signal to background ratio with GBCAs can become critically low.

Fluorine and iron-oxide contrast media are alternatives for vascular MRI in molecular imaging and angiographic applications. Fluorine contrast media can be visualized without generating any signal from the background tissue. Iron-oxides are known for the strong contrast effect, which is typically much higher than for GBCAs.

Although fluorine contrast media require no background suppression due to the absence of background signal from tissue, signal levels are relatively low with respect to proton MR, which requires longer acquisition times to generate sufficient signal. Iron-oxide based contrast agents on the other hand, generate a strong image contrast, which however is usually a negative (hypointense) contrast effect. This thesis studies the feasibility of fluorine and iron-oxide, as alternative vascular MRI contrast media, and complementary MR imaging techniques.

Main findings

A fluorine contrast medium was used for MR angiography to benefit from the absence of tissue background signal. Due to the intrinsically low signal levels of fluorine MR, the acquisition time is usually long, presenting practical problems with long stay of patients in the MRI scanner. In this thesis, a conventional MR sequence for fluorine MR was used, followed by super-resolution reconstruction post-processing techniques. These post-processing techniques enable to reduce the acquisition time, while maintaining at least the same spatial resolution and signal-to-noise ratio with respect to a conventional 3D fluorine MR acquisition. The reduction of scan time is an important factor to facilitate clinical translation.

The use of iron-oxides was applied to visualize the growth of novel blood vessels, i.e. angiogenesis, in fast growing tumors. Iron-oxides usually demonstrate a hypointense contrast (i.e. signal loss) on regular MR images. We showed that a positive contrast technique can be used to depict iron-oxide contrast hyperintensities and to highlight regions of angiogenesis. Positive contrast enhancement methods can be applied as image post-processing techniques on conventional diagnostic images that depict the

anatomy, which means that the application does not increase the examination time. This is a strong advantage and an important factor for clinical translation.

In this thesis targeted fluorine nanoparticles were applied as a contrast medium to visualize ex vivo thrombi. The molecular target, α -2-antiplasmin, is only active when a thrombus is probably still susceptible to thrombolysis, and is therefore expected to be a good indicator for the decision to treat a blood clot or not. In ex vivo MRI measurements the fluorine α -2-antiplasmin targeted contrast medium could differentiate specifically targeted and control targeted uptake. The in vivo detection of the targeted and control targeted contrast media remains challenging and requires further improvements before it can be used.

Target population

The future target population of the current research work are patients that suffer from cardiovascular diseases. In this thesis, it was shown that advanced contrast agents can be used to study the normal and diseased vasculature. The advantage of fluorine contrast media to depict the vasculature, separately from the organs and other structures, is that it enables a clear delineation of the vessel lumen (where contrast resides) from the background signal. Also the applicability of molecular targeted contrast media, for detection of blood clots or angiogenesis, is potentially beneficial for future patients. Eventually, both fluorine and iron-oxide contrast media may contribute to more sensitive and more specific detection and visualization of pathological processes, even before symptoms or structural abnormalities can be noticed. Furthermore, the possibility to visualize the anatomy and molecular targeted contrast media in a “one-stop shop” examination and the absence of ionizing radiation makes MR imaging attractive for screening and follow-up procedures.

The studies of this thesis and its results are also relevant for the healthcare industry. On the one side for the hospitals in terms of cost reduction (reduced acquisition time) and on the other side for the pharmaceutical industry regarding development of novel contrast media and also vendors of MRI systems and image processing software. Hospitals could benefit from the use of iron-oxide contrast media for clinical molecular MR imaging, because of its high sensitivity. This diagnostic exam can result in additional value in the same MR session and therefore save on equipment and/or time on a multi-modality diagnostic imaging with PET or SPECT. Naturally, this has to be weighed against the additional costs of the contrast media and this is where the development of contrast media suitable for molecular MR imaging becomes interesting for the healthcare industry. MR imaging is suitable for screening and follow-up studies, due to the lack of ionizing radiation, but well-developed clinical applications for molecular imaging are still lacking.

In clinical research there is a shift towards use of (ultra-)high-field MR systems, which may provide new applications for advanced contrast media and diagnostic imaging. However, the current generation GBCAs have a low efficiency at high-field. The novel

contrast media used in this thesis will benefit from a stronger magnetic field and will therefore be even more valuable in (ultra-)high-field MRI applications.

Innovation and future

This thesis focuses on imaging innovations with iron-oxides and fluorine based contrast media for vascular MRI. Although the research performed was of pre-clinical nature, the ultimate goal is translation and clinical implementation. We found that, with the combination of iron oxide labeled particles and positive contrast techniques, angiogenesis could be visualized in spite of the small size of the target blood vessels. Tumor angiogenesis is a sign of tumor malignancy and molecular MRI, targeted to the activated endothelium, may provide valuable diagnostic information with a minimally invasive technique. The use of iron-oxide contrast media is probably closest to a broad clinical acceptance, as it has already been used in (non-molecular) contrast media MRI applications in clinical studies.

For fluorine contrast media, this thesis shows the strengths and weaknesses of fluorine imaging and its potential in the detection of abnormalities of the pathologic vascular system. However, the absence of clinically available contrast media and the limited availability of clinical fluorine MR acquisition technology (e.g. RF components and pulse sequences) hamper clinical translation. The in vivo detection of fluorine particles with MR is usually based on the fluorine spin density, which requires that the local concentration of fluorine needs to be rather high in comparison to GBCAs or iron-oxide particles. In clinical trials, fluorine is therefore primarily used for human cell tracking studies, where the cells are loaded with fluorine prior to injection. For fluorine imaging, dedicated (radiofrequency) hardware is required, which is also a hurdle to perform fluorine imaging on clinical MR systems. These aspects hamper the translation of experimental fluorine imaging to clinical applications. This thesis shows the potential of fluorine imaging and its potential benefits for the patient. Despite the fact that all essential elements of fluorine MR imaging, such as contrast media and fluorine capable MRI systems are available, major steps still need to be taken to increase the sensitivity of fluorine detection before real clinical applications become feasible.

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